ClinicalEvidence

Warts (non-genital)

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ABSTRACT

INTRODUCTION: Warts are caused by the human papillomavirus (HPV), of which there are over 100 types. HPV probably infects the skin via areas of minimal trauma. Risk factors include use of communal showers, occupational handling of meat, and immunosuppression. In immunocompetent people, warts are harmless and resolve as a result of natural immunity within months or years. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of treatments for warts (non-genital)? We searched: Medline, Embase, The Cochrane Library, and other important databases up to October 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 17 studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic, review we present information relating to the effectiveness and safety of the following interventions: intralesional bleomycin; intralesional candida antigen; contact immunotherapy; cryotherapy; duct tape occlusion; photodynamic treatment; pulsed dye laser; surgical procedures; and topical salicylic acid.

QUESTIONS

INTERVENTIONS

Key points

- Warts are caused by the human papillomavirus (HPV), of which there are over 100 types. HPV probably infects the skin via areas of minimal trauma.

  Risk factors include use of communal showers, occupational handling of meat, and immunosuppression.

  In immunocompetent people, warts are harmless and resolve as a result of natural immunity within months or years.

  For what is such a common condition, there are few large, high-quality RCTs available to inform clinical practice.
- Topical salicylic acid increases the cure rate of warts compared with placebo.
- Cryotherapy may be as effective at increasing the cure rate of warts as topical salicylic acid, but we don't know about wart recurrence. We found insufficient evidence on the effects of cryotherapy versus placebo.
- Contact immunotherapy with dinitrochlorobenzene may increase wart clearance compared with placebo, but it can cause inflammation.
- We don't know whether intralesional bleomycin speeds up clearance of warts compared with placebo, as studies have given conflicting results.
- We found no systematic reviews or RCTs about the effects of intralesional candida antigens.
- We don't know whether duct tape occlusion, pulsed dye laser, photodynamic treatment, or surgery increase cure rates compared with placebo, as few high-quality studies have been found.
- We found limited evidence from one small RCT that photodynamic treatment plus topical salicylic acid may increase the proportion of warts cured compared with placebo plus topical salicylic acid; however, it may increase pain or discomfort compared with placebo.

DEFINITION Non-genital warts (verrucas) are an extremely common, benign, and usually a self-limited skin disease. Infection of epidermal cells with the human papillomavirus (HPV) results in cell proliferation and a thickened, warty papule on the skin. There are over 100 different types of HPV. The appearance of warts is determined by the type of virus and the location of the infection. Any area of skin

can be infected, but the most common sites are the hands and feet. Genital warts are not covered in this review (see review on Genital warts). We have also excluded RCTs in people with immunosuppression in this review. **Common warts** are most often seen on the hands and present as skin-coloured papules with a rough 'verrucous' surface. **Flat warts** are most often seen on the backs of the hands and on the legs. They appear as slightly elevated, small plaques that are skin-coloured or light brown. **Plantar warts** occur on the soles of the feet and look like very thick callouses.

INCIDENCE/ PREVALENCE

There are few reliable, population-based data on the incidence and prevalence of non-genital warts. Prevalence probably varies widely between different age groups, populations, and periods of time. Two large population-based studies found prevalence rates of 0.84% in the US [1] and 12.9% in Russia. [2] Prevalence is highest in children and young adults, and two studies in school populations have shown prevalence rates of 12% in 4- to 6-year-olds in the UK [3] and 24% in 16- to 18-year-olds in Australia. [4]

AETIOLOGY/ RISK FACTORS

Warts are caused by HPV, of which there are over 100 different types. They are most common at sites of trauma, such as the hands and feet, and probably result from inoculation of virus into minimally damaged areas of epithelium. Warts on the feet can be acquired from walking barefoot in areas where other people walk barefoot. One observational study (146 adolescents) found that the prevalence of warts on the feet was 27% in those that used a communal shower room and 1.3% in those that used the locker (changing) room. [5] Warts on the hand are also an occupational risk for butchers and meat handlers. One cross-sectional survey (1086 people) found that the prevalence of warts on the hand was 33% in abattoir workers, 34% in retail butchers, 20% in engineering fitters, and 15% in office workers. [6] Immunosuppression is another important risk factor. One observational study in immunosuppressed renal transplant recipients found that, at 5 years or longer after transplantation, 90% had warts. [7]

PROGNOSIS

Non-genital warts in immunocompetent people are harmless and usually resolve spontaneously as a result of natural immunity within months or years. The rate of resolution is highly variable and probably depends on several factors, including host immunity, age, HPV type, and site of infection. One cohort study (1000 children in long-stay accommodation) found that two-thirds of warts resolved without treatment within a 2-year period. [8]

AIMS OF INTERVENTION

To eliminate warts, with minimal adverse effects.

OUTCOMES

Wart clearance (generally accepted as complete eradication of warts from the treated area); reduction in number of warts (if wart clearance not reported); **wart recurrence**; and **adverse effects** of treatment.

METHODS

Clinical Evidence search and appraisal October 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to October 2013, Embase 1980 to October 2013, and The Cochrane Database of Systematic Reviews 2013, issue 9 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) Database. We also searched for retractions of studies included in the review. Titles and abstracts identified by the initial search, run by an information specialist, were first assessed against predefined criteria by an evidence scanner. Full texts for potentially relevant studies were then assessed against predefined criteria by an evidence analyst. Studies selected for inclusion were discussed with an expert contributor. All data relevant to the review were then extracted by an evidence analyst. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in the English language, blinded or open label trials, studies of any size of which more than 80% of participants were followed up. There was a minimum follow-up of 4 weeks. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 27). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of treatments for warts (non-genital)?

OPTION SALICYLIC ACID (TOPICAL)

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- Topical salicylic acid increases the cure rate of warts compared with placebo.

Benefits and harms

Topical salicylic acid versus placebo or no treatment:

We found one systematic review (search date 2011), [9] which identified six RCTs (486 people) comparing topical salicylic acid with placebo or no treatment.

Wart clearance

Topical salicylic acid compared with placebo or no treatment Topical salicylic acid may be more effective than placebo at increasing the cure rate of warts (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	486 people with warts 6 RCTs in this analysis	**Cure rate , timeframe unclear** 137/242 (57%) with topical salicylic acid 91/244 (37%) with placebo	RR 1.56 95% CI 1.20 to 2.03 P <0.001 Results should be interpreted with caution; see Further information on studies	●○○	topical salicylic acid

Wart recurrence

No data from the following reference on this outcome. [9]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[9] Systematic review	People with warts (number not clear)	**Adverse effects** with topical salicylic acid with placebo or no treatment Topical salicylic acid was associated with minor skin irritation in some of the RCTs			

Topical salicylic acid versus cryotherapy:

See option on Cryotherapy, p 5 .

Further information on studies

[9] One of the five RCTs included in the meta-analysis compared topical salicylic acid plus lactic acid versus placebo, and one compared topical salicylic acid plus monochloroacetic acid crystals versus placebo. The RCTs varied in their study design and methodology, and only one RCT was classified as having a high methodological quality. Trial heterogeneity and poor quality of the RCTs included in the review mean that the pooled results should be treated with caution.

Comment: None.

OPTION CONTACT IMMUNOTHERAPY (DINITROCHLOROBENZENE)

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- Contact immunotherapy with dinitrochlorobenzene may increase wart clearance compared with placebo, but it can cause inflammation.

Benefits and harms

Contact immunotherapy (dinitrochlorobenzene) versus placebo or no treatment:

We found one systematic review (search date 2011), [9] which identified two RCTs (80 people) comparing contact immunotherapy (dinitrochlorobenzene) versus placebo.

Wart clearance

Contact immunotherapy compared with placebo or no treatment Contact immunotherapy using dinitrochlorobenzene may be more effective at increasing the proportion of people with wart clearance (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	80 people 2 RCTs in this analysis	**Proportion of people with wart clearance , end of trial** 32/40 (80%) with contact immunotherapy (dinitrochlorobenzene 2% solution followed by 1% solution) 15/50 (38%) with placebo or no treatment The end of the trial was 4 months in 1 RCT and unspecified in the other	RR 2.12 95% CI 1.38 to 3.26 NNT 2 95% CI 2 to 4 1 RCT included in the meta-analysis was published in only abstract form [10]	●●○	contact immunotherapy

Wart recurrence

No data from the following reference on this outcome. [9]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[11] RCT	People with warts In review [9]	**Adverse effects** with contact immunotherapy (dinitrochlorobenzene)			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		with placebo or no treatment The RCT found that 6/20 (30%) people developed an inflammatory reaction to dinitrochlorobenzene 2% solution only after the second application, but that all these people subsequently experienced significant local irritation with or without blistering when treated with dinitrochlorobenzene 1% solution No one withdrew from the study			

Comment: We found one systematic review [9] that identified one RCT comparing dinitrochlorobenzene with cryotherapy; however, the data were published in only abstract form, which does not meet our reporting criteria and so is not discussed further.

OPTION CRYOTHERAPY

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- Cryotherapy may be as effective at increasing the cure rate of warts as topical salicylic acid, but we don't know about wart recurrence.
- We found insufficient evidence on the effects of cryotherapy versus placebo.

Benefits and harms

Cryotherapy versus placebo or no treatment:

We found one systematic review (search date 2011), [9] which identified three RCTs (227 people), and one subsequent RCT [12] comparing cryotherapy versus topical placebo cream or no treatment.

Wart clearance

Cryotherapy compared with placebo or no treatment We don't know whether cryotherapy is more effective than placebo at increasing the cure rate of warts after 2 to 4 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	227 people 3 RCTs in this analysis	**Cure rate , 2 to 4 months** 41/107 (38%) with cryotherapy 26/120 (22%) with placebo	RR 1.45 95% CI 0.65 to 3.23 P = 0.36	⟷	Not significant
[12] RCT **3-armed trial**	12 people; 2 warts each treated	**Cure rate , timeframe unclear** 2/12 (17%) with cryotherapy 3/8 (38%) with placebo The remaining arm assessed photodynamic treatment of 4 warts Participants were followed up for up to 5 visits, which were 2 to 4 weeks apart	Significance not assessed		

Wart recurrence

No data from the following reference on this outcome. [9] [12]

Adverse effects

No data from the following reference on this outcome. [9] [12]

Cryotherapy versus photodynamic treatment:

We found one systematic review (search date 2011), [9] which identified one RCT (30 people) [13] and one subsequent RCT [12] comparing cryotherapy versus photodynamic treatment.

Wart clearance

Cryotherapy compared with photodynamic treatment Cryotherapy may be less effective than photodynamic treatment at reducing the number of warts after 4 to 6 weeks in people who also used topical salicylic acid plus lactic acid; however, evidence was weak. We don't know about wart clearance (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[13] RCT **5-armed trial**	30 adults with recalcitrant hand and foot warts of different sizes and categories In review [9]	**% reduction in number of warts , 4 to 6 weeks** 20% with cryotherapy 73% with 3 episodes of white light photodynamic treatment Absolute numbers not reported The remaining arms assessed 1 episode of white light photodynamic treatment, 3 episodes of red light photodynamic treatment, and 3 episodes of blue light photodynamic treatment All patients were free to use a combination of topical lactic acid and salicylic acid during the RCT Cryotherapy was liquid nitrogen spray applied for about 10 seconds from whitening of the wart area, which was then allowed to thaw before repeating, applied up to 4 times within 2 months	P <0.01	○○○	white light photodynamic treatment
[13] RCT **5-armed trial**	30 adults with recalcitrant hand and foot warts of different sizes and categories In review [9]	**% reduction in number of warts , 4 to 6 weeks** 20% with cryotherapy 71% with 1 episode of white light photodynamic treatment Absolute numbers not reported The remaining arms assessed 3 episodes of white light photodynamic treatment, 3 episodes of red light photodynamic treatment, and 3 episodes of blue light photodynamic treatment	Reported as significant; P value not reported	○○○	white light photodynamic treatment

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		All patients were free to use a combination of topical lactic acid and salicylic acid during the RCT Cryotherapy was liquid nitrogen spray applied for about 10 seconds from whitening of the wart area, which was then allowed to thaw before repeating, applied up to 4 times within 2 months			
[13] RCT **5-armed trial**	30 adults with recalcitrant hand and foot warts of different sizes and categories In review [9]	**% reduction in number of warts , 4 to 6 weeks** 20% with cryotherapy 42% with 3 episodes of red light photodynamic treatment Absolute numbers not reported The remaining arms assessed 3 episodes of white light photodynamic treatment, 1 episode of white light photodynamic treatment, and 3 episodes of blue light photodynamic treatment All patients were free to use a combination of topical lactic acid and salicylic acid during the RCT Cryotherapy was liquid nitrogen spray applied for about 10 seconds from whitening of the wart area, which was then allowed to thaw before repeating, applied up to 4 times within 2 months	P = 0.03		red light photodynamic treatment
[13] RCT **5-armed trial**	30 adults with recalcitrant hand and foot warts of different sizes and categories In review [9]	**% reduction in number of warts , 4 to 6 weeks** 20% with cryotherapy 28% with 3 episodes of blue light photodynamic treatment Absolute numbers not reported The remaining arms assessed 3 episodes of white light photodynamic treatment, 1 episode of white light photodynamic treatment, and 3 episodes of red light photodynamic treatment All patients were free to use a combination of topical lactic acid and salicylic acid during the RCT Cryotherapy was liquid nitrogen spray applied for about 10 seconds from whitening of the wart area, which was then allowed to thaw before repeating, applied up to 4 times within 2 months	P = 0.03		blue light photodynamic treatment
[12] RCT **3-armed trial**	12 people; 2 warts each treated	**Cure rate , timeframe unclear** 1/4 (25%) with aminolaevulinic acid plus blue light (5 treatments at 2–4 week intervals) 2/12 (17%) with cryotherapy The remaining arm assessed placebo photodynamic treatment for 8 warts Participants were followed up for up to 5 visits, which were 2–4 weeks apart	Significance not assessed		

Wart recurrence

No data from the following reference on this outcome. [12] [13]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[13] RCT **5-armed trial**	30 adults with recalcitrant hand and foot warts of different sizes and categories In review [9]	**Adverse effects** with cryotherapy with 3 episodes of white light photodynamic treatment with 1 episode of white light photodynamic treatment with 3 episodes of red light photodynamic treatment with 3 episodes of blue light photodynamic treatment 1 person receiving cryotherapy withdrew because of pain Photodynamic treatment was associated with burning and itching during the first few minutes of treatment and mild discomfort throughout treatment in all people receiving it 3 people discontinued photodynamic treatment because of intolerable pain during the first minutes after exposure			

No data from the following reference on this outcome. [12]

Cryotherapy versus intralesional bleomycin:

See option on Intralesional bleomycin, p 16 .

Cryotherapy versus topical salicylic acid:

We found one systematic review (search date 2011), [9] which identified four RCTs (707 people), and one subsequent RCT [14] comparing cryotherapy versus topical salicylic acid.

Wart clearance

Cryotherapy compared with topical salicylic acid Cryotherapy and topical salicylic acid seem to be equally effective at increasing wart cure rate at 3 to 6 months (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	707 people 4 RCTs in this analysis	**Cure rate , 3 to 6 months** 153/351 (44%) with cryotherapy 126/356 (35%) with topical salicylic acid	RR 1.23 95% CI 0.88 to 1.71 P = 0.22	⟷	Not significant
[14] RCT	193 people aged 12 years and over with warts	**Cure rate , at 6 months** 33/98 (34%) with cryotherapy 29/95 (31%) with salicylic acid	Difference –3.1% 95% CI –10% to +16.3% P = 0.64	⟷	Not significant

Wart recurrence

Cryotherapy compared with topical salicylic acid We don't know how effective cryotherapy is compared with salicylic acid at reducing the recurrence of warts at 6 months in people who had previously had complete wart clearance with either cryotherapy or salicylic acid (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart recurrence					
[14] RCT	240 people, aged 12 years and over, with warts who had previously had complete wart clearance	**Recurrence , at 6 months** 15/110 (13.6%) cleared at 12 weeks with cryotherapy; 2 recurred at 6 months 17/119 (14.3%) cleared at 12 weeks with salicylic acid; 2 recurred at 6 months The study looked at plantar warts only	Significance not assessed		

No data from the following reference on this outcome. [9]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[14] RCT	240 people aged 12 years and over with warts	**Treatment-related adverse events** 2/110 (2%) blisters larger than expected with cryotherapy 0/119 with salicylic acid	Significance not assessed		
[15] RCT	75 people with common warts	**Pain** 29/37 (78%) with cryotherapy 5/38 (13%) with salicylic acid	P <0.001	○○○	salicylic acid
[15] RCT	77 people with plantar warts	**Pain** 31/37 (84%) with cryotherapy 4/40 (10%) with salicylic acid	P <0.001	○○○	salicylic acid
[15] RCT	75 people with common warts	**Blisters** 22/37 (59%) with cryotherapy 2/38 (5%) with salicylic acid	P <0.001	○○○	salicylic acid

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[15] RCT	77 people with plantar warts	**Blisters** 16/37 (43%) with cryotherapy 5/40 (13%) with salicylic acid	P = 0.003	○○○	salicylic acid

No data from the following reference on this outcome. [9]

Cryotherapy plus salicylic acid versus salicylic acid alone:

We found one systematic review (search date 2011), [9] which identified two RCTs (318 people) comparing cryotherapy plus salicylic acid versus topical salicylic acid alone.

Wart clearance

Cryotherapy plus salicylic acid compared with topical salicylic acid alone Cryotherapy plus salicylic acid may be more effective than salicylic acid alone at improving wart clearance at 3 to 6 months. However, evidence was weak (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	318 people 2 RCTs in this analysis	**Cure rate , 3 to 6 months** 125/163 (77%) with cryotherapy plus salicylic acid 96/155 (62%) with salicylic acid alone Unspecified blinding in 1 RCT; hand warts only in 1 RCT	RR 1.24 95% CI 1.07 to 1.43 P = 0.0042	●○○	Cryotherapy plus salicylic acid

Wart recurrence

No data from the following reference on this outcome. [9]

Adverse effects

No data from the following reference on this outcome. [9]

Cryotherapy plus salicylic acid versus cryotherapy alone:

We found one systematic review (search date 2011), [9] which identified two RCTs (328 people) comparing cryotherapy plus salicylic acid versus cryotherapy alone.

Wart clearance

Cryotherapy plus salicylic acid compared with cryotherapy alone We don't know whether cryotherapy plus salicylic acid is more effective than cryotherapy alone at improving wart clearance at 3 to 6 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	328 people 2 RCTs in this analysis	**Cure rate , 3 to 6 months** 125/163 (77%) with cryotherapy plus salicylic acid 107/165 (65%) with cryotherapy alone Unspecified blinding in 1 RCT; hand warts only in 1 RCT	RR 1.20 95% CI 0.99 to 1.45 P = 0.058	⟷	Not significant

Wart recurrence

No data from the following reference on this outcome. [9]

Adverse effects

No data from the following reference on this outcome. [9]

Cryotherapy versus duct tape occlusion:

See option on Duct tape occlusion, p 20 .

Aggressive versus gentle cryotherapy:

We found one systematic review (search date 2011), [9] which identified four RCTs (592 people) comparing aggressive cryotherapy versus gentle cryotherapy.

Wart clearance

Aggressive cryotherapy compared with gentle cryotherapy Aggressive cryotherapy (not further defined) may be more effective than gentle cryotherapy (not further defined) at increasing the proportion of people with wart clearance after 1 to 3 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	592 adults 4 RCTs in this analysis	**Proportion of people with wart clearance , 1 to 3 months** 159/304 (52%) with aggressive cryotherapy 89/288 (31%) with gentle cryotherapy	RR 1.90 95% CI 1.15 to 3.15 NNT 5 95% CI 3 to 7 For details of methodological limitations, see Further information on studies	●○○	aggressive cryotherapy

Wart recurrence

No data from the following reference on this outcome. [9]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[16] RCT	200 people with warts	**Pain or blistering** 64/100 (64%) with aggressive cryotherapy 44/100 (44%) with gentle cryotherapy 5 people withdrew from the aggressive group and 1 from the gentle group because of pain and blistering	RR 1.45 95% CI 1.12 to 2.31 NNH 5 95% CI 3 to 15	●○○	gentle cryotherapy

Interval between cryotherapy:

We found one systematic review (search date 2011), [9] which identified three RCTs (313 people) comparing intervals of cryotherapy.

Wart clearance

More frequent cryotherapy compared with less frequent cryotherapy We don't know how cryotherapy given more frequently compares with cryotherapy given less frequently (2 weeks apart *v* 3 weeks apart) at improving wart clearance after 3 to 8 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	313 people 3 RCTs in this analysis	**Proportion of people with wart clearance , 3 to 8 months** 77/158 (49%) with 2-week interval between cryotherapy treatments 70/155 (45%) with 3-week interval between cryotherapy treatments	RR 1.03 95% CI 0.77 to 1.37	⟷	Not significant

Wart recurrence

No data from the following reference on this outcome. [9]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[17] RCT	People with warts In review [9]	**Proportion of people with pain, blistering, or both** 29% with cryotherapy at 1-weekly intervals	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		7% with cryotherapy at 2-weekly intervals 0% with at 3-weekly intervals			

Further information on studies

[9] Aggressive versus gentle cryotherapy: definitions of 'aggressive' and 'gentle' differed between RCTs in the systematic review, and some RCTs included warts that were resistant to treatment and others did not. In one RCT, all people received topical salicylic acid plus lactic acid and, in another, people in the aggressive treatment group received lactic acid whereas people in the gentle treatment group did not. The review reported that "although these trials were in different populations, on different types of warts and used different definitions of aggressive and gentle, it was felt that the results could be usefully combined for analysis".

Comment:

The evidence from available RCTs about cryotherapy is both limited and contradictory. Heterogeneity of study design, methodology, and the populations included make it extremely difficult to draw firm conclusions. [9] For example, some RCTs identified by the review included all types of wart on the hands and feet in all age groups, whereas others were more selective and simply looked at hand warts, or excluded certain groups such as mosaic plantar warts or warts that were resistant to treatment. Of particular note is the likelihood that wart-clinic populations used for these RCTs might have had different characteristics in different periods of time. For instance, hospital-based studies carried out in the 1970s in the UK would have included a higher proportion of people with warts that had never been treated before — which have a greater chance of cure, spontaneous resolution, or both. In the 1980s and 1990s, more people with warts were being treated in primary care; consequently, the people included in hospital-based RCTs were more likely to have warts resistant to treatment, with correspondingly lower cure rates. Hence, strong evidence for the beneficial effect of cryotherapy is difficult to establish. However, the review identified evidence that aggressive cryotherapy is beneficial. We found one RCT identified by the systematic review [9] that assessed the effect of duration of cryotherapy; however, it did not meet our reporting criteria and is not discussed further here. See Comment in Contact immunotherapy (dinitrochlorobenzene), p 4 . The majority of the trials included in the systematic review had unclear or inadequate allocation concealment. The review stated that the beneficial effects of treatment in these trials were likely to have been overstated.

Clinical guide:

Taking these factors into account, cryotherapy is likely to be beneficial for people with non-genital warts where first-line treatment with topical salicylic acid has failed. Depending on the site, size, and status of the person, cryotherapy of different degrees of aggressiveness can be delivered at different time intervals.

OPTION PHOTODYNAMIC TREATMENT

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- We don't know whether photodynamic treatment is more effective than placebo.
- We found limited evidence from one small RCT that photodynamic treatment plus topical salicylic acid may increase the proportion of warts cured compared with placebo plus topical salicylic acid.
- Photodynamic treatment may increase pain or discomfort compared with placebo.

Benefits and harms

Photodynamic treatment versus placebo photodynamic treatment:

We found one systematic review (search date 2011) [9] of photodynamic treatment, which identified one RCT (45 people) [18] and one subsequent RCT (12 people) [12] comparing photodynamic treatment versus placebo photodynamic treatment.

Wart clearance

Photodynamic treatment compared with placebo photodynamic treatment We don't know whether photodynamic treatment is more effective than placebo. Aminolaevulinic acid photodynamic treatment plus topical salicylic acid may be more effective than placebo photodynamic treatment plus topical salicylic acid at increasing the proportion of people with wart clearance after 18 weeks in people with warts unsuccessfully treated for over 3 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[18] RCT	45 adults with warts unsuccessfully treated for >3 months In review [9]	**Proportion of warts cured , 18 weeks** 64/114 (56%) with aminolaevulinic acid photodynamic treatment plus topical salicylic acid 47/113 (42%) with placebo photodynamic treatment plus topical salicylic acid	P <0.05	○○○	aminolaevulinic acid photodynamic treatment plus topical salicylic acid
[12] RCT	12 people; 2 warts each treated	**Cure rate , timeframe unclear** 1/4 (25%) with 20% aminolaevulinic acid plus 417 nm blue light (5 treatments at 2–4-week intervals) 3/8 (38%) with placebo photodynamic treatment The remaining arm assessed cryotherapy for 12 warts Participants were followed up for up to 5 visits that were 2–4 weeks apart	P = 0.2	⟷	Not significant

Wart recurrence

No data from the following reference on this outcome. [12] [18]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT	45 adults with warts unsuccessfully treated for >3 months In review [9]	**Painful warts (pain ranging from light to unbearable) , immediately after treatment** 17% with aminolaevulinic acid photodynamic treatment plus topical salicylic acid 4% with placebo photodynamic treatment plus topical salicylic acid Absolute numbers not reported Burning and itching continued for up to 48 hours in some people	Significance not assessed		

No data from the following reference on this outcome. [12]

Different types of photodynamic treatment versus each other:

We found one systematic review (search date 2011), [9] which identified one RCT. [19]

Wart clearance

Different types of photodynamic treatment compared with each other We don't know how proflavine photodynamic treatment and neutral red photodynamic treatment compare at improving wart clearance after 8 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[19] RCT **3-armed trial**	56 people In review [9]	**Proportion of people with wart clearance , 8 weeks** 10/27 (37%) with proflavine photodynamic treatment 10/23 (43%) with neutral red photodynamic treatment The remaining arm assessed placebo Matched pairs of warts on the left and right hands were treated with photodynamic treatment or placebo In people who responded to photodynamic treatment, the warts on the placebo-treated side also resolved	Significance not assessed		

Wart recurrence

No data from the following reference on this outcome. [19]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[19] RCT **3-armed trial**	56 people In review [9]	**Adverse effects** with proflavine photodynamic treatment with neutral red photodynamic treatment The remaining arm assessed placebo The RCT found no adverse effects associated with photodynamic treatment			

Photodynamic treatment versus cryotherapy:

See option on Cryotherapy, p 5 .

Comment: None.

OPTION BLEOMYCIN (INTRALESIONAL)

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- We don't know whether intralesional bleomycin speeds up clearance of warts compared with placebo, as studies have given conflicting results.

Benefits and harms

Intralesional bleomycin versus placebo:

We found one systematic review (search date 2011, 4 RCTs, 133 people) [9] comparing intralesional bleomycin versus placebo. The systematic review did not perform a meta-analysis because of heterogeneity among RCTs.

Wart clearance

Intralesional bleomycin compared with placebo We don't know whether intralesional bleomycin is more effective at increasing the proportion of people with wart clearance, or at increasing the number of warts cured, after 6 weeks to 3 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[20] RCT	24 adults with warts unsuccessfully treated for >3 months; matched pairs of warts on the left and right side of the body In review [9]	**Proportion of people with a more favourable response (not defined) , 6 weeks** 21/24 (88%) with bleomycin 3/24 (13%) with saline placebo	P <0.001	○○○	bleomycin 0.1%
[20] RCT	24 adults with warts unsuccessfully treated for >3 months; matched pairs of warts on the left and right side of the body In review [9]	**Proportion of warts cured , 6 weeks** 34/59 (58%) with bleomycin 6/59 (10%) with saline placebo	P <0.001	○○○	bleomycin 0.1%
[21] RCT	16 people In review [9]	**Proportion of warts cured , 6 weeks** 31/38 (82%) with bleomycin 16/46 (34%) with placebo Local anaesthetic was used routinely before the injection of bleomycin	P <0.001 Results should be interpreted with caution; RCT randomised number of people but analysed number of warts	○○○	bleomycin 0.1%
[22] RCT **4-armed trial**	62 adults In review [9]	**Proportion of warts cured , 3 months** 4/22 (18%) with bleomycin in saline 5/22 (23%) with bleomycin in sesame oil 8/19 (42%) with saline placebo 5/11 (46%) with sesame-oil placebo	P = 0.018 for combined results for bleomycin *v* combined results for placebo Results should be interpreted with caution; RCT randomised number of people but analysed number of warts	○○○	placebo

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[23] RCT	31 people In review [9]	**Proportion of people with wart clearance , 30 days** 15/16 (94%) with bleomycin 11/15 (73%) with placebo Local anaesthetic was used routinely before the injection of bleomycin	RR 1.28 95% CI 0.92 to 1.78 P = 0.15	⟷	Not significant

Wart recurrence

No data from the following reference on this outcome. [20] [21] [22] [23]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[20] RCT	24 adults with warts unsuccessfully treated for >3 months; matched pairs of warts on the left and right side of the body In review [9]	**Adverse effects** with bleomycin with saline placebo 1 person withdrew because of pain during injection, and 1 because of pain after injection The RCT reported that pain was experienced by most people (no further data reported)			
[21] RCT	16 people In review [9]	**Adverse effects** with bleomycin with placebo Despite the routine use of local anaesthetic before the injection of bleomycin, pain was experienced by most people (no further data reported)			
[22] RCT **4-armed trial**	62 adults In review [9]	**Adverse effects** with bleomycin in saline with bleomycin in sesame oil with saline placebo with sesame-oil placebo The RCT reported dullness, pain, swelling, or bleeding in 19/62 (31%) participants, but it did not specify which treatment they received			

No data from the following reference on this outcome. [23]

Different concentrations of intralesional bleomycin:

We found one systematic review (search date 2011), [9] which identified one RCT comparing different concentrations of intralesional bleomycin. [24]

Wart clearance

Different concentrations of intralesional bleomycin versus each other We don't know how different concentrations of intralesional bleomycin compare at improving wart clearance at 3 months (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[24] RCT **3-armed trial**	26 adults In review [9]	**Proportion of warts cured (defined as disappearance of warts after 1 to 3 treatments and no recurrence within 3 months after treatment) , 3 months** 11/15 (73%) with bleomycin 0.25% 26/30 (86%) with bleomycin 0.5% The third arm evaluated bleomycin 1.0% See Further information on studies for reasons for variation in number of warts assessed	P >0.05 for bleomycin 0.25% *v* bleomycin 0.5%	⟷	Not significant
[24] RCT **3-armed trial**	26 adults In review [9]	**Proportion of warts cured (defined as disappearance of warts after 1–3 treatments and no recurrence within 3 months after treatment) , 3 months** 11/15 (73%) with bleomycin 0.25% 25/34 (74%) with bleomycin 1.0% The third arm assessed bleomycin 0.5% See Further information on studies for reasons for variation in number of warts assessed	P >0.05 for bleomycin 0.25% *v* bleomycin 1.0%	⟷	Not significant
[24] RCT **3-armed trial**	26 adults In review [9]	**Proportion of warts cured (defined as disappearance of warts after 1–3 treatments and no recurrence within 3 months after treatment) , 3 months** 26/30 (86%) with bleomycin 0.5% 25/34 (74%) with bleomycin 1.0% The third arm assessed bleomycin 0.25% See Further information on studies for reasons for variation in number of warts assessed	P >0.05 for bleomycin 0.5% *v* bleomycin 1.0%	⟷	Not significant

Wart recurrence

No data from the following reference on this outcome. [24]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[24] RCT **3-armed trial**	26 adults In review [9]	**Adverse effects** with bleomycin 0.25% with bleomycin 0.5% with bleomycin 1.0% The RCT reported pain at the injection site in most people, irrespective of dose (no further data reported)			

Intralesional bleomycin versus cryotherapy:

We found one systematic review (search date 2011), [9] which identified two RCTs [25] [26] comparing intralesional bleomycin versus cryotherapy.

Wart clearance

Intralesional bleomycin compared with cryotherapy Intralesional bleomycin may be more effective at increasing the proportion of people with wart clearance after 6 weeks. However, evidence came from one small RCT and evidence was weak (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[25] RCT	44 people above 12 years of age with warts on symmetric limbs In review [9]	**Proportion of people with wart clearance , 6 weeks** 38/44 (87%) with bleomycin 30/44 (68%) with cryotherapy Intralesional bleomycin and cryotherapy were randomly allocated to either right- or left-sided warts	RR 1.27 95% CI 1.0 to 1.6 P <0.05 Results should be interpreted with caution; see Further information on studies for full details	●○○	bleomycin
[26] RCT	73 people In review [9]	**Cure , 8 weeks after last treatment** 37/39 (95%) with bleomycin 0.1% 26/34 (77%) with cryotherapy (1–4 sessions)	Significance not assessed Bleomycin reported as more effective but no RR or P value reported		

Wart recurrence

No data from the following reference on this outcome. [9] [25]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[25] RCT	44 people above 12 years of age	**Adverse effects** with bleomycin			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	with warts on symmetric limbs	with cryotherapy The RCT reported adverse effects in 5 people: in 3 people who received intralesional bleomycin and in 2 who received cryotherapy (details not reported)			
[26] RCT	73 people In review [9]	**Pain hampering routine activities , (few minutes to 3 days)** 2/39 (5%) with bleomycin 4/34 (12%) with cryotherapy	Significance not assessed		

Further information on studies

[24] The disparity in the number of warts assessed in each group could be explained by the exclusion of warts that spontaneously regressed from the analysis, and by a high withdrawal rate in people receiving intralesional bleomycin 0.25%.

[25] The results should be interpreted with caution, as important parameters such as wart size and duration of disease were not mentioned. Furthermore, the clinical importance of the difference between treatments may not have been detected due to the small sample size.

Comment: None.

OPTION CANDIDA ANTIGEN (INTRALESIONAL) New

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- We found no systematic review or RCTs about the effects of intralesional candida antigens.

Benefits and harms

Intralesional candida antigen versus placebo:

We found no systematic review or RCTs.

Comment: None.

OPTION DUCT TAPE OCCLUSION

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- We don't know whether duct tape increases cure rates compared with placebo, as few high-quality studies have been found.

Benefits and harms

Duct tape occlusion versus placebo:

We found one systematic review (search date 2011), [9] which identified two RCTs comparing duct tape occlusion with placebo.

Wart clearance

Duct tape occlusion compared with placebo We don't know whether duct tape occlusion is more effective than placebo at increasing the proportion of people with wart clearance after 6 to 24 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[9] Systematic review	193 people 2 RCTs in this analysis 1 RCT included children aged 4 to 12 years; 1 RCT included adults	**Cure rate , 6 to 24 weeks** 16/95 (17%) with duct tape 12/98 (12%) with placebo	RR 1.43 95% CI 0.51 to 4.05 P = 0.50	⟷	Not significant

Wart recurrence

Duct tape occlusion compared with placebo We don't know whether duct tape occlusion is more effective than placebo at reducing the proportion of people with recurrence after 6 months in people who had previously had complete wart clearance with either duct tape occlusion or placebo (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart recurrence					
[27] RCT	17 adults who had complete wart clearance at 2 months In review [9] Subgroup analysis 90 adults with warts were initially treated	**Proportion of people with wart recurrence , 6 months** 6/8 (75%) with clear duct tape occlusion 3/9 (33%) with placebo	P = 0.15	⟷	Not significant

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[28] [29] RCT	103 children aged 4–12 years In review [9]	**Skin rash** 7/47 (15%) with clear duct tape occlusion 0/52 (0%) with placebo	P = 0.14	⟷	Not significant
[27] RCT	90 adults In review [9]	**Adverse effects** with clear duct tape occlusion with placebo 1 person in the duct tape occlusion group had numbness in their finger because of the dressing, and 1 person in the placebo group had bleeding			

Duct tape occlusion versus cryotherapy:

We found one systematic review (search date 2005), [9] which identified one RCT. [30]

Wart clearance

Duct tape occlusion compared with cryotherapy We don't know how duct tape occlusion and cryotherapy compare at improving wart clearance after 2 months (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[30] RCT	61 people aged 3 to 22 years In review [9]	**Proportion of people with complete resolution of warts , 8 weeks** 22/26 (85%) with duct tape occlusion for 6 days a week plus gentle debridement once a week 15/25 (60%) with cryotherapy for 10 seconds every 2 to 3 weeks plus gentle debridement up to 6 treatments Completer analysis: 51/61 (84%) of people were followed up	P = 0.05 RCT had methodological limitations; see Further information on studies for details	⟷	Not significant
[30] RCT	61 people aged 3 to 22 years In review [9]	**Proportion of people with complete resolution of warts , 8 weeks** 22/30 (73%) with duct tape occlusion for 6 days a week plus gentle debridement once a week 15/31 (48%) with cryotherapy for 10 seconds every 2 to 3 weeks plus gentle debridement up to 6 treatments Intention-to-treat analysis: 51/61 (84%) of people were followed up	RR 1.52 (calculated by review) [9] 95% CI 0.99 to 2.31	⟷	Not significant

Wart recurrence

No data from the following reference on this outcome. [9]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[30] RCT	61 people aged 3 to 22 years In review [9]	**Adverse effects** with duct tape occlusion for 6 days a week plus gentle debridement once a week with cryotherapy for 10 seconds every 2 to 3 weeks plus gentle debridement up to 6 treatments The RCT found that people having duct tape occlusion had skin irritation and difficulty in keeping the tape on, and all people having cryotherapy had mild-to-severe pain (absolute numbers not reported) 51/61 (84%) of people were followed up			

Further information on studies

[30] Despite the careful randomisation and blinding in the RCT comparing duct tape occlusion with cryotherapy, the numbers were small. Furthermore, an unspecified number of outcome assessments were carried out over the telephone over the 2 months' follow-up, and it was not entirely clear how long after the treatment period these assessments were done.

Comment: There is insufficient evidence to indicate that duct tape occlusion is effective in wart clearance.

OPTION PULSED DYE LASER

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- We don't know whether pulsed dye laser increases cure rates compared with placebo, as few high-quality studies have been found.

Benefits and harms

Pulsed dye laser versus placebo:

We found one systematic review (search date 2011), [9] which identified one RCT [31] of pulsed dye laser. The systematic review found no RCTs comparing pulsed dye laser versus placebo. [9]

Wart clearance

Pulsed dye laser compared with placebo We don't know whether pulsed dye laser is more effective than placebo at increasing the proportion of people with wart clearance after 14 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Wart clearance					
[31] RCT	37 people aged 19 to 70 years In review [9]	**Proportion of people with complete wart clearance , 14 weeks** 6/19 (32%) with pulsed dye laser at 595 nm (spot size 5 mm, impulse duration 0.45 ms, flux 9 J/cm^2 with 5 passes at a frequency of 1 Hz) 3/16 (19%) with placebo	P = 0.46 Results should be interpreted with caution; see Further information on studies for full details	⟷	Not significant

Wart recurrence

No data from the following reference on this outcome. [31]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[31]	37 people aged 19 to 70 years	**Incidence of crust and purpura**	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
RCT	In review [9]	11% with pulsed dye laser at 595 nm (spot size 5 mm, impulse duration 0.45 ms, flux 9 J/cm^2 with 5 passes at a frequency of 1 Hz) 0% with placebo Absolute numbers not reported			
[31] RCT	37 people aged 19 to 70 years In review [9]	**Pain levels (measured on a 10-point visual analogue scale)** 4.7 with pulsed dye laser at 595 nm (spot size 5 mm, impulse duration 0.45 ms, flux 9 J/cm^2 with 5 passes at a frequency of 1 Hz) 1.5 with placebo	Significance not assessed		
[31] RCT	37 people aged 19 to 70 years In review [9]	**Tolerance (measured on a 10-point visual analogue scale)** 8.31 with pulsed dye laser at 595 nm (spot size 5 mm, impulse duration 0.45 ms, flux 9 J/cm^2 with 5 passes at a frequency of 1 Hz) 9.81 with placebo	Significance not assessed		

Further information on studies

[31] The results of the RCT should be interpreted with caution, as the clinical importance of the difference between treatments may not be detected owing to the small sample size. Important parameters, such as wart size and duration in each group, were also not mentioned.

Comment: None.

OPTION SURGICAL PROCEDURES (CAUTERY AND CURETTAGE, CARBON DIOXIDE LASER FOR CAUTERISATION ONLY)

- For GRADE evaluation of interventions for Warts (non-genital), see table, p 27 .
- We don't know whether surgery increases cure rates compared with placebo, as no high-quality studies have been found.

Benefits and harms

Surgery:

We found one systematic review (search date 2011), which identified no RCTs. [9]

Comment: None.

GLOSSARY

Contact immunotherapy Contact sensitisers such as dinitrochlorobenzene, diphencyprone, and squaric acid dibutyl ester result in allergic dermatitis, which stimulates an immune reaction in close proximity to the wart.

Cryotherapy A destructive treatment based on the targeted freezing of tissue using liquid nitrogen, dimethyl ether propane, or carbon dioxide snow. Liquid nitrogen achieves the lowest temperatures and is now the most commonly used agent.

Photodynamic treatment Combines the application of a photosensitising substance (usually aminolaevulinic acid) to the wart and subsequent irradiation with wavelengths of light that are absorbed by the photosensitising substance and lead to destruction of the target tissue.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Candida antigen (intralesional) New option. Categorised as unknown effectiveness.

Contact immunotherapy (dinitrochlorobenzene) One systematic review updated. [9] Categorisation unchanged (likely to be beneficial).

Cryotherapy One systematic review updated, [9] and one subsequent RCT added. [12] Categorisation unchanged (likely to be beneficial).

Duct tape occlusion One systematic review updated. [9] Categorisation unchanged (unknown effectiveness).

Intralesional bleomycin One systematic review updated. [9] Categorisation unchanged (unknown effectiveness).

Topical salicylic acid One systematic review updated. [9] Categorisation unchanged (beneficial).

Photodynamic treatment One systematic review updated, [9] and one subsequent RCT added. [12] Categorisation changed from likely to be beneficial to unknown effectiveness.

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Warts (non-genital)

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Competing interests: YMT and KFL declare that they have no competing interests.

Disclaimer

GRADE **Evaluation of interventions for Warts (non-genital).**

Important outcomes			Wart clearance, Wart recurrence						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of treatments for warts (non-genital)?									
6 (486) [9]	Wart clearance	Topical salicylic acid versus placebo or no treatment	4	–1	0	–2	0	Very low	Quality point deducted for weak methods; directness points deducted for inclusion of co-interventions and trial heterogeneity
2 (80) [9]	Wart clearance	Contact immunotherapy (dinitrochlorobenzene) versus placebo or no treatment	4	–2	0	–1	+1	Low	Quality points deducted for sparse data and inclusion of abstract in analysis; directness point deducted for unclear length of follow-up in 1 RCT; effect-size point added for RR >2
4 (247) [9] [12]	Wart clearance	Cryotherapy versus placebo or no treatment	4	–1	0	–2	0	Very low	Quality point deducted for weak methods; directness points deducted for no statistical analyses between groups in 1 RCT and for unclear length of follow-up in 1 RCT
2 (42) [12] [13]	Wart clearance	Cryotherapy versus photodynamic treatment	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for inclusion of co-interventions
5 (900) [9] [14]	Wart clearance	Cryotherapy versus topical salicylic acid	4	–1	0	0	0	Moderate	Quality point deducted for weak methods
1 (240) [14]	Wart recurrence	Cryotherapy versus topical salicylic acid	4	0	0	–2	0	Low	Directness points deducted for no statistical analysis between groups and for inclusion of plantar warts only
2 (318) [9]	Wart clearance	Cryotherapy plus salicylic acid versus salicylic acid alone	4	–1	0	–1	0	Low	Quality point deducted for unspecified blinding in 1 RCT; directness point deducted for inclusion of hand warts only in 1 RCT
2 (328) [9]	Wart clearance	Cryotherapy plus salicylic acid versus cryotherapy alone	4	–1	0	–1	0	Low	Quality point deducted for unspecified blinding in 1 RCT; directness point deducted for inclusion of hand warts only in 1 RCT
4 (592) [9]	Wart clearance	Aggressive versus gentle cryotherapy	4	–1	0	–2	0	Very low	Quality point deducted for weak methods; directness points deducted for different definitions of aggressive and gentle between RCTs, and inclusion of co-interventions
3 (313) [9]	Wart clearance	Interval between cryotherapy	4	–1	0	–1	0	Low	Quality point deducted for weak methods; directness point deducted for differences in populations
2 (57) [12] [18]	Wart clearance	Photodynamic treatment versus placebo photodynamic treatment	4	–2	0	–1	0	Very low	Quality point deducted for sparse data and incomplete reporting of results; directness point deducted for inclusion of co-interventions
1 (56) [19]	Wart clearance	Different types of photodynamic treatment versus each other	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results; directness point deducted for no statistical analysis between groups

Important outcomes			Wart clearance, Wart recurrence						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
4 (133) [20] [21] [22] [23]	Wart clearance	Intralesional bleomycin versus placebo	4	–1	–1	–2	0	Very low	Quality point deducted for sparse data; consistency point deducted for conflicting results; directness points deducted for combined control group, and randomising by people but analysing by warts
1 (26) [24]	Wart clearance	Different concentrations of intralesional bleomycin	4	–3	0	0	0	Very low	Quality points deducted for sparse data, exclusion of warts that spontaneously regressed from the analysis, and a high withdrawal rate in people receiving intralesional bleomycin 0.25%
2 (117) [25] [26]	Wart clearance	Intralesional bleomycin versus cryotherapy	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for no statistical analysis between groups in 1 RCT
2 (193) [9]	Wart clearance	Duct tape occlusion versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for age differences between populations
1 (17) [27]	Wart recurrence	Duct tape occlusion versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data; directness point deducted for subgroup analysis
1 (61) [30]	Wart clearance	Duct tape occlusion versus cryotherapy	4	–2	0	0	0	Low	Quality points deducted for sparse data and poor outcome assessment
1 (37) [31]	Wart clearance	Pulsed dye laser versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and not specifying number of warts per treatment group at baseline

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.